REMARKS/ARGUMENTS

The Claim Amendments

It is observed that the data reported in the application prove that the inventive freeze-dried form of the cyclodextrin/carotenoid complexes had improved bioavailability compared to other forms, *e.g.*, spray-dried cyclodextrin/carotenoid complexes. Nevertheless, the claims are amended herewith to remove the "improving the bioavailability" language found objectionable by the Examiner. The claims now read as originally filed, so no new matter is added by virtue of these amendments and their entry respectfully requested.

SUMMARY OF THE CLAIM REJECTIONS

A. Claims 1-3 and 5

Claims 1-3 and 5 stand rejected under the provisions of 35 U.S.C. § 102(b) as being unpatentable over Szente (*J. Incl. Phen.*, 1998).

B. Claims 1, 2, and 5-7

Claims 1, 2 and 5-7 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Szente in view of Hedges (*Chem. Rev.*, 1998).

C. Claims 1-3 and 6

Claims 1-3, and 6 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Olmedilla (*Clin. Sci.*, 2002) in view of Pfitzner (*BBA*, 2000).

D. Claim 4

Claim 4 stands rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Olmedilla in view of Pfitzner in further view of Kulevskaya (*Pharm. Chem. J.*, 2002).

E. Claims 5 and 7

Claims 5 and 7 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Olmedilla in view of Pfitzner in further view of Szente.

F. Claim 9

Claim 9 stands rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Olmedilla in view of Pfitzner in further view of Sharper (*Manufacturing and Formulation*, 2001).

G. Claims 8 and 10

Claims 8 and 10 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Olmedilla in view of Pfitzner in further view of Szente in further view of Kulevskaya and Sharper.

H. Claims 11-13, 15-17, and 19

Claims 5 and 7 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Olmedilla in view of Pfitzner, Sharper and Mele (*Carbohyd. Res.*, 2002).

I. Claims 14, 18, and 20

Claims 14, 18, and 20 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Olmedilla in view of Pfitzner, Sharper, and Mele, in further view of Kulevskaya.

J. Claims 1-3

Claims 1-3 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 3 and 9 of copending application serial no. 10/309,999.

SUMMARY OF THE CITED ART

1. Szente

The product described in the present application is different from Szente and the results on bioavailability unanticipated for the following reasons. Szente describes complexation of β-carotene with different cyclodextrins. There is no information on other carotenes or xanthophylls.

It is well known in the field of cyclodextrins, that formation of inclusion complexes and improvement in properties, such as bioavailability and solubility of the active molecule, is highly variable and unpredictable. It also is known that the different cyclodextrins used in the current application have different properties in terms of cavity size, hydrophobicity, and molecular

weight. They interact differently with the same active hydrophobic molecule, are stereo-selective, and some may form the inclusion complex while others may not interact.

The hydrocarbon carotenoids (β-Carotene and lycopene) are less polar, as compared to the xanthophylls (lutein and zeaxanthin), and may differ in their affinity towards cyclodextrins. Even within the same class, for example xanthophylls, lutein and zeaxanthin are stereoisomers, which may have different affinities for a cyclodextrin. It also has been reported that complexation of astaxanthin, another xanthophyll, with sulfobutyl ether beta-cyclodextrin does not improve the solubility to result in a pharmaceutically acceptable chemical delivery system for humans. The authors conclude that the increased aqueous solubility may be useful in introducing astaxanthin into mammalian cell culture systems (Lockwood, S.F., O'Mailey, S., and Mosher, G.L., "Improved aqueous solubility of crystalline astaxanthin by Captisol", *J. Pharm Sci.*, 92: 922-6, 2003).

Complexation with cyclodextrins often may not result in increased bioavailbility *in vivo*. For example, according to Spirichev, *et al.* (1996) uptake of β-carotene from a cyclodextrin complex was lower as compared to the commercial oil dispersions or microencapsulated beadlets in human studies (Spirichev, V.B., Iakushina, L.A., Isaeva, V.A., Shkarina, T.N., Malakhova, E.A., and Poznanskaia, A.A., "Study of bioavailability of different forms of synthetic beta-carotene in volunteers", *Vopr. Pitan.*, 6: 22-6, 1996; article in Russian).

The properties of the complexes described by Szente can be used as an example to illustrate the unpredictable nature of the cyclodextrin complexes. In their studies, improved heat stability of β-carotene was observed with α-CD, γ-CD, DIMEB, and per-O-acetyl-β-CD, while the β-CD complex was <u>not</u> stable. The stability of the β-CD complex was similar to uncomplexed β-carotene adsorbed onto zeolite. Also α-CD was most effective in stabilizing β-carotene. α-CD has the smallest cavity size, as compared to β-CD or γ-CD, and is not expected to form better inclusion complexes with carotenes. The light stability of the complexes also varies based on the cyclodextrin used for complexation. The light stability follow the rank order of α-CD > methyl-β-CD > acetyl β-CD > γ-CD > β-CD. Szente also states that the good complex forming property of the carotenoids, however, does not always manifest in the improved chemical stability of the complexed colorant (see, section 5.1.)

The peanut oil-β-carotene-cyclodextrin complexes described by Szente are a ternary complex between the three components. The complexation reaction is carried out in the presence of peanut oil. Szente's results indicate that the properties of the carotene/CD complex are modified when there is a ternary complexation with an oil. The present application

describes a physical dispersion of the dry carotenoid cyclodextrin complex in oil. There is **no** complexation between the oil and the cyclodexrin carotenoid complexes and no such oil complex is claimed.

The Examiner's comments regarding product-by-process claims are interesting, but inapposite. The Examiner fails to grasp that Applicants' product in claims 1-3 and 5 is a **different** product than the same complex recovered by, for example, spray drying, as amply demonstrated in the working examples in the above-identified application.

It is clear that Szente does not anticipate claims 1-3 and 5 as Szente shows a ternary complex, unless Applicants' binary complex, and Szente fails to show a freeze-dried binary complex as claimed.

2. Basu

The composition disclosed by Basu is a complex of canola oil with cyclodextrins. The oil is added to the cyclodextrin and the reaction carried out until the complexation is complete. The various components of the oil, such as, *inter alia,* triglycerides, tocopherols, carotenoids, and sterols, interact with cyclodextrins and form non-specific binary and ternary complexes, based on degree of affinity, hydrophobicity, and other properties. This composition is very similar to the product disclosed in U.S. Patent No. 6,025,510, entitled "Process for stabilizing and dispersing vegetable oils which contain polyunsaturated fatty acid radicals by means of γ-cyclodextrin" (Wimmer, *et al.*, 2000). Also, according to Basu, in his composition most of the cyclodextrin cavities were occupied by the sterols.

As such, the product describe is entirely different than the present application, where Applicants disclose a specific complexation between a purified carotenoid and cyclodextrins. The oil used for formulation does **not** form a binary or ternary complex with cyclodextrins. As such, Basu does not anticipate claims 1, 2, and 5-7.

3. Hedges

Hedges teaches the general principles of manufacturing with cyclodextrins. With respect to recovery techniques, Hedges teaches at p. 2036 under the heading, "E. Drying of Complexes", extensively discusses heating for recovery, *viz.*, "tray dryer, spray dryer, fluid bed dryer, or vacuum-dryer can be used." Freeze-drying is mentioned in passing onto when a "glass or very hard complex requiring milling" results from drying at which time freeze-drying can be used. As such, Hedges only strengthens Applicants' novel freeze-dried cyclodextrin/carotenoid complexes, as Hedges in concert with art does **not** recognize that novel

and different chemical/physical properties can be result depending upon which method of drying is used. Unless these various techniques are actually tried and compared, it is impossible to predict this very unexpected development. Again, the Examiner respectfully is requested to review the extensive data in the application whereat the novel properties of the freeze-dried cyclodextrin/carotenoid complexes are reported.

4. Olmedilla

Olmedilla teaches the use of lutein in oil capsules for supplementation. It is well known in the industry that carotenoids are used either in oil formulations or as microencapsulated beadlets in supplements. The oil formulations are used in soft gelatin capsules while the beadlets are used in hard gelatin capsules or tablets. It also is known in the art that the carotenoids are better absorbed in the presence of lipids. The teachings of Olmedilla do not indicate that a cyclodextrin complex of the carotenoid can be formulated for soft gelatin capsules or that it remains bioavailable *in vivo* after formulation. Olmedilla does not teach the inter-individual variations in the uptake of lutein from oil dispersions. The complexation with various cyclodextrins and the bioavailability of the complexes as described Applicants are not anticipated or obvious based on Olmedila.

5. Pfitzner

Pfitzner describes a soluble complex of carotenoids with methyl-β-cyclodetxrin (~2% active in the complex). Their results indicate variations in the stability and complexation ability of the carotenoids, even when the same cyclodextrin is used for complexation. Zeaxanthin was less stable as a complex than when dissolved in organic solvents. The authors were unable to explain the reason for this destabilizing action of the cyclodextrin. The carotenoids also showed different complexation abilities with the cyclodextrin. The low complexation of lycopene was attributed to its aliphatic structure and physicochemical properties. Pfitzner does not teach the uptake of lutein, lycopene, or zeaxanthin by the cells. They describe the uptake of β-carotene from the inclusion complex. However, there is no indication that complexation improves the bioavailability to the extent that it can be used as a supplement. And the uptake of β-carotene was **not** improved as compared to the commercial oil dispersions or microencapsulated beadlets in human studies.

6. Kelevskaya

Lecithin is one of the commonly used excipients in formulations for soft gelatin capsules. Kulevskaya reports increased stability of β-carotene by phospholipids. They also quote Proskuryakov *et al.* (2002) for increased bioavailability of the carotene by phospholipids. The carotene was dissolved in lecithin in these studies. Lecithin also has been reported to lower the uptake of carotenoids (β-carotene and lutein) solubilized in mixed micelles by Caco2 cells and in animal studies (Baskaran *et al.*, 2003).

In the present application, the lutein cyclodextrin complex was not solubilized in lecithin. Lecithin was used as an excipient to facilitate formulation for soft gelatin capsules. Fig. 5 in the application shows the uptake of lutein solubilized in lecithin, as compared to the uptake from the lecithin-oil dispersed cyclodextrin complex of lutein in caco2 cells. Combined with Fig. 2, it is clear that the uptake is improved with complexation, as compared to the lecithin liposome.

The excipients used in soft gelatin formulations can interact with the cyclodextrin complex. Being strong solvents, MCT and polysorbate 80 may extract the carotenoids from the inclusion complex, while components of lecithin have been reported to form inclusion complexes with cyclodextrin (Xie *et al.*, 2001; Anderson *et al.*, 2004). The studies by Kulevskaya do **not** indicate whether a carotenoid cyclodextrin complex retains its properties on formulation with lecithin and oil.

7. Mele

It is not obvious from Mele, that freeze-drying is the preferred method for drying the carotenoid cyclodextrin complex. There is no experimental evidence on the bioavailability of the complex versus other methods of drying in their publication. They are mainly focused on physicochemical characterization of the complex prepared by freeze-drying, often used in the laboratory for drying small samples.

8. Sharper

The teachings of Sharper are well known in the art. Carotenoids have been formulated in soft gelatin capsules for a number of years. The variations in lutein uptake from an oil dispersion has been reported by, for example, Bowen *et al.* Applicants have shown an improvement in the uptake of lutein from the cyclodextrin complex–oil soft gelatin capsules, as compared to free lutein–oil soft gelatin capsules. Also, cyclodextrin complexes in general are mainly used in hard gelatin capsules and tablets as the active compound is stabilized by

cyclodextrins. Since the carotenoid complexes were not stable, Applicants formulated them for soft gelatin capsules.

2. Copending Application USSN '999

While it still is Applicants' position that this is not available as a reference, the present invention clearly is patentable over the disclosure of this application. That is, the '999 application only enables spray drying and equates all forms of drying, including freeze-drying. Thus, there is no way that the inventors of the '999 application could have known that freeze-drying would be so superior to the forms of drying. Data testifying to this fact has been presented and not rebutted.

While Applicants believe that the foregoing results alone deserve patent protection, there in one more element in independent claims 1 and 11 that also needs to be discussed—the excipient of choice: "a vegetable oil". USSN '999 discloses coatings, which may be "an oil, a natural polymer or a synthetic polymer." (¶ 012 in USSN '999). The data in Example 5 in the present application states that, "freeze-dried lutein/γ-cyclodextrin complex was formulated with medium chain triglycerides (MCT), polysorbate 80, and a combination of lecithin-soybean oil. The formulations were dispersed in PBS and treated with lipase to simulate the digestive process before incorporation into the culture medium." The results reported in Table 5 show both 6-hour and a 24-hour incubation cellular lutein uptake percent increases that are from about 8 to 15 times more uptake at 6 hours and from almost 4 to about 34 times more uptake at 24 hours. Again, while vegetable oil excipients are known in the art, the unexpected bioavailability of freeze-dried carotenoid/cyclodextrin complexes with vegetable oil excipients, as set forth in the claims under examination, is not known in the art. Importantly, also, there is no disclosure in the art that would lead the skilled artisan to predict that freeze-drying in combination with a vegetable oil would result in improved bioavailability.

Thus, the present claims, then, are patentable over USSN '999, which only claims a "coated carotenoid formulation in powder form".

THE REJECTIONS OF THE CLAIMS

A. The 102(b) Rejection of Claims 1-3 and 5 over Szente

Initially, claim 1 includes two components: a freeze-dried cyclodextrin/carotenoid complex in a molar ratio of between about 0.5:1 and 10:1; and a vegetable oil. Again and contrary to the position espoused by the Examiner, Applicants have amply demonstrated that their composition and its properties, quite unexpectedly, are dependent upon the method of

recovering the cyclodextrin/carotenoid complex. The law recognizes that a composition and its properties are inseparable.

The Examiner is reminded of the working example in the present application. For example, in Example 1, Applicants directly compared spray-dried lutein/γ-cyclodextrin complex with the novel freeze-dried lutein/γ-cyclodextrin complex with respect to cellular lutein uptake by Caco2 cells. The results are tabulated in Table 1 at pg. 10 as follows:

TABLE 1
Effect of Drying on the Uptake of Lutein from the Lutein/γ-Cyclodextrin Complex by Caco2 Cells

Sample	Cellular Lutein Uptake (Percent Increase)	
	6-hr Incubation	24-hr incubation
Spray-dried Lutein/γ-cyclodextrin Complex	8.75	14.35
Freeze-dried Lutein/γ-cyclodextrin Complex	20.5	56.1

The above-tabulated data from the present application testifies to the fact that the inventive composition of claim 1 has different properties imparted by dint of its method of recovery. This data testifies to the fact that Applicants have a different composition. The Examiner's position that all cyclodextrin/carotenoid complexes have the same properties regardless of their method of recovery is a generalization proven untrue for the composition of claim 1. In fact, such data underscores the unexpectedness of the inventive composition of claim 1. Novelty, then, is proven.

B The 103(a) Rejection of Claims 1, 2, and 5-7 over Szente and Hedges

Szente, as demonstrated above, does not anticipate nor render obvious the claims under examination. Hedges is cited for showing common methods of drying cyclodextrin/carotenoid complexes. However, none of those common methods involves freeze-drying. As argued and demonstrated above, all methods of recovering cyclodextrin/carotenoid complexes are not equivalent when it comes to cellular bioavailability.

This combination, then, shows a ternary complex recovered by spray drying or other drying technique that specifically excludes freeze-drying. As stated above, claim 1 does not go to a ternary complex that includes a vegetable oil; but, rather, to a binary complex and a vegetable oil excipient. As such, these claims are not rendered unpatentable over the cited combination.

C. The 103(a) Rejection of Claims 1-3 and 6 over Olmedilla and Pfitzner

It seems appropriate at this juncture to review the unpredictability of carotenoids and especially complexes of carotenoids. The Examiner is reminded of the prior declarations of Dr. Madahvi, one of the Applicants. In particular, Dr. Madhavi's first declaration (submitted with Applicants' December 21, 2004 response) noted that the weak cyclodextrin/carotenoid bonds could be disrupted by a number of factors, including, *inter alia*, excipients used in formulations, including, *inter alia*, vegetable oils, medium chain triglycerides, and synthetic surfactants such as polysorbates, polyethylene glycols, and phospholipids such as lecithin. She continued that excipients with different polarities could interact with cyclodextrins resulting in the dissociation of the complex, inhibit the release of the actives, or modulate the dissolution properties. The interactions in general are often unpredictable in her expert opinion. Dr. Madhavi cites several publications on the interactions of cyclodextrin inclusion complexes of pharmaceuticals and flavor compounds with formulation excipients.

Again, the art combination structured in the claims rejections do not provide the certainty in teaching regarding the vegetable oil portion of the inventive product and process insofar as expected stability of the complex is concerned, nor the freeze-drying recovery of the carotenoid complex, nor importantly the combination of freeze-drying and use of vegetable oil.

With respect to the drying method used in forming the complex, Dr. Madhavi emphasized the data reported in the working examples in the above-identified application. She stated that the invention describes a commercially efficient process, which includes freeze-drying an aqueous dispersion of carotenoid-cyclodextrin complex. Freeze-drying was found to be efficient as compared to spray-drying with a 95% recovery of the product, as compared to 50% loss (recovery) with spray-drying. Further, to her surprise, the freeze-dried product was superior to spray dried product in bioavailability studies. This unexpectedness is not dispelled or compromised just because freeze-drying is known in the art. The unexpectedness is that for Applicants' product only freeze-drying provided improved bioavailability for the product along with improved yields of product. Such unexpectedness testifies to the invention.

The teachings of Olmedilla, then, do not indicate that a cyclodextrin complex of the carotenoid can be formulated for soft gelatin capsules or that it remains bioavailable *in vivo* after formulation. Olmedilla does not teach the inter-individual variations in the uptake of lutein from oil dispersions. The complexation with various cyclodextrins and the bioavailability of the complexes as described Applicants are not anticipated or obvious based on Pfitzner and Olmedila.

On the other hand, a combination of Pfitzner, Spirichev, and Lockwood, demonstrate the unpredictable nature of cyclodextrin complexes of carotenoids. And studies by Bowen *et al.* (2002) show the poor and variable uptake of free lutein from oil dispersions in a human study.

D. The 103(a) Rejection of Claim 4 over Omedilla, Pfitzner and Kulevskaya

Claim 1 has been shown to be patentable over Omedilla and Pfitzner. The addition of Kulevskaya does not add any vitality to such cited combination. As stated above with respect to Kulevskaya, Kulevskaya reports dissolving carotene in lecithin. However, lecithin also has been reported to lower the uptake of carotenoids (β-carotene and lutein) solubilized in mixed micelles by Caco2 cells and in animal studies (Baskaran *et al.*, 2003). For purposes of claim 4, the lutein cyclodextrin complex was **not** solubilized in lecithin. Lecithin was used as an excipient to facilitate formulation for soft gelatin capsules. Fig. 5 in the application shows the uptake of lutein solubilized in lecithin as compared to the uptake from the lecithin-oil dispersed cyclodextrin complex of lutein in caco2 cells. Combined with Fig. 2, it is clear that the uptake is improved with complexation as compared to the lecithin liposome.

This combination, then, fails to render obvious claim 4.

E. The § 103(a) Rejection of Claims 5 and 7 over Omedilla, Pfitzner and Szente

Claim 1 has been shown to be patentable over Omedilla and Pfitzner. The deficiencies of Szente also have been uncovered above. The combination, then, fails to render unpatentable claims 5 and 7.

F. The § 103(a) Rejection of Claim 9 over Omedilla, Pfitzner and Sharper

Claim 1 has been shown to be patentable over Omedilla and Pfitzner. Sharper adds nothing of value to the basic composition in claim 1. Applicants are not claiming soft gelatin capsules *per se*; but, rather, freeze-dried cyclodextrin/carotenoid complexes plus vegetable oils, where such composition is disposed in a soft gelatin capsule. Sharper does not make up for the glaring deficiencies in the Omedilla and Pfitzner combination. Claim 9, then, is patentable.

G. The § 103(a) Rejection of Claims 8 and 10 over Omedilla, Pfitzner, Szente, Kulevskaya and Sharper

Each of these citations and their combination have been discussed adequately above. These claims stand patentable over this cited combination.

H. The § 103(a) Rejection of Claims 11-13, 15-17, ad 19 over Omedilla, Pfitzner, Sharper, and Mele

Dealing with the soft gel issue (claim 11) initially, Dr. Madhavi noted in her declaration, *ibid*, that it is well known in the art that hydrophobic compounds present delivery challenge,s because of their physicochemical properties and soft gelatin capsules may offer a delivery system. However, complexation of carotenoids with cyclodextrins in general resulted in a hydrophilic, water dispersible fine powder. Such complexes have been used for making directly compressible tablets or incorporated in to hard gelatin capsules, as cyclodextrins are expected to stabilize sensitive compounds against degradation. However, Dr. Madhavi and her co-inventor found that complexation with cyclodextrins did **not** stabilize the carotenoids to afford the necessary commercially accepted shelf life in tablets or hard capsules. The soft-gelatin formulation was developed to stabilize the carotenoids. Again, this cannot be predicted and is unexpected, especially when combined with freeze-drying and use of a vegetable oil to disperse the carotenoid complex.

Dr. Madhavi further stated in her first declaration that when hydrophobic excipients, such as vegetable oils, are used, they may inhibit the dispersion of the complex in water; thus, reducing the uptake of the active molecule. However, to her surprise, she found that the complex retained its properties even after formulation with vegetable oil or vegetable oil-lecithin as excipients.

Dr. Madhavi concluded that, in her opinion, it was totally unexpected that a commercially feasible, practical, and commercially viable process resulted for making a bioavailable cyclodextrin/carotenoid complex by freeze-drying a cyclodextrin/carotenoid complex in a molar ratio of between about 0.5:1 and 10:1, and adding such freeze-dried complex to a vegetable oil. Converting such complex to a soft gelatin capsule (claim 11) even further defines the invention over the cited art combination. The art cited simply does not render obvious the present invention in her expert opinion.

Again, while the individual pieces of claim 11 are individually known in the art, it has been beyond the skilled artisan to recognize the combination of such individual pieces and the

totally unexpected results realized by such combination. The working examples in the application demonstrate such unexpected results. The combination claimed cannot be predicted from the art and especially the properties of such combination. Dr. Madhavi testifies to this in her declaration. Such declaration and its statements go unchallenged.

I. The § 103(a) Rejection of clams 14,18, and 20 over Olmedilla, Pfitzner, Sharper, Mele, and Kulevskaya

The discussion of claim 4 above applies equally here.

J. The Provisional Rejection of Claims 1-3 over USSN 10/309,999

Initially, the Examiner is informed that claim 1 in '999 has been amended to be limited to a coated carotenoid formulation "in powder form". The Examiner is reminded of Dr. Madhavi's declaration discussed above and especially that complexation of carotenoids with cyclodextrins in general resulted in a hydrophilic, water dispersible fine powder. Such complexes have been used for making directly compressible tablets or incorporated in to hard gelatin capsules, as cyclodextrins are expected to stabilize sensitive compounds against degradation. However, Dr. Madhavi and her co-inventor found that complexation with cyclodextrins did not stabilize the carotenoids to afford the necessary commercially accepted shelf life in tablets or hard capsules. The soft-gelatin formulation was developed to stabilize the carotenoids. As such, claim 1 defines over '999, is an unexpected improved over '999, and, thus, is patentable over '999.

SUMMARY

In view of the remarks, previously submitted declarations, claim amendments, and the remarks herewith, allowance of all claims and passage to issue of this application respectfully is requested.

Respectfully submitted,

Date: 28 June 2006

Jerry K. Mueller, Jr.
Reg. No. 27,576
MUELLER AND SMITH, L.P.A.
Mueller-Smith Building
7700 Rivers Edge Drive
Columbus, Ohio 43235-1355

Tel.: 614-436-0600
Fax: 614-436-0057
email: *smueller@muellersmith.com*

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited on June 28, 2006, with the United States Postal Service as first class mail in an envelope addressed to:

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Jane Keeney